Mortality Associated With Pulmonary Hypertension in Congenital Rubella Syndrome

**AUTHORS:** Michiko Tozumi, MD, a,b Hideki Motomura, MD, a,d Hien Minh Vo, MD, e Kensuke Takahashi, MD, f Enga Pham, MD, f Hien Anh Thi Nguyen, MSc, h Tho Huu Le, MD, PhD, i Masahiro Hashizume, MD, PhD, i,j Koya Ariyoshi, MD, PhD, i,j Duc Anh Dang, PhD, h Hiroyuki Moriuchi, MD, PhD, c,d and Lay-Myint Yoshida, MD, PhD

Departments of a Pediatric Infectious Diseases and Clinical Medicine, Institute of Tropical Medicine, and Departments of b Tropical Pediatric Infectious Diseases, c Pediatrics, and d Clinical Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan; e Department of Pediatrics, Khanh Hoa University Hospital, Khanh Hoa, Vietnam; f Department of Pediatrics, Khanh Hoa General Hospital, Nha Trang, Vietnam; g Department of Bacteriology, National Institute of Hygiene and Epidemiology, Hanoi, Vietnam; and h Department of Planning and Research Collaboration, Khanh Hoa Health Service, Nha Trang, Vietnam

**ABSTRACT**

Outbreaks of rubella and congenital rubella syndrome (CRS) continue to arise in various countries where a rubella-containing vaccine is not included in the national immunization program. After a large-scale rubella outbreak in 2011, CRS cases emerged in Vietnam. The aim of this study was to clarify the clinical features of these cases with an emphasis on cardiovascular complications and outcomes.

**OBJECTIVE:** Outbreaks of rubella and congenital rubella syndrome (CRS) continue to arise in various countries where a rubella-containing vaccine is not included in the national immunization program. After a large-scale rubella outbreak in 2011, CRS cases emerged in Vietnam. The aim of this study was to clarify the clinical features of these cases with an emphasis on cardiovascular complications and outcomes.

**METHODS:** From October 2011 to September 2012, we conducted a prospective surveillance study of infants <12 months of age who had manifestations suggesting CRS at the only referral hospital in Khanh Hoa Province. These infants underwent standard examinations, echocardiography, cranial ultrasonography, automated auditory brainstem responses, blood cell count measurements, and rubella-specific antibody testing. Detected cardiovascular defects were regularly followed with echocardiography.

**RESULTS:** We enrolled 38 cases of CRS characterized by a low birth weight (71%), cardiovascular defects (72%), cataracts (13%), hearing impairment (93%), purpura (84%), hepatosplenomegaly (68%), and thrombocytopenia (76%). Patent ductus arteriosus, the most common cardiovascular complication, was often associated with progressive pulmonary hypertension (PH). As of January 2013, 13 infants (34%) had died, and PH was significantly more frequent among the fatalities (P = .004); however, therapeutic closure of the ductus reversed the PH in several cases.

**CONCLUSIONS:** PH-associated mortality is high among infants who have CRS in Vietnam. Providing proper assessments, continuous follow-up, and timely intervention for cardiovascular defects is critical for the management of CRS patients. Echocardiography is of diagnostic and prognostic value and can support better clinical management of CRS, even in a developing country setting. Pediatrics 2014;134:e519–e526

**WHAT’S KNOWN ON THIS SUBJECT:** Few studies have performed precise cardiovascular assessments and regular follow-up of congenital rubella syndrome (CRS) patients’ clinical courses. A few studies have reported mortalities among children who have CRS; however, the causes of death have not been precisely described.

**WHAT THIS STUDY ADDS:** A total of 38 CRS cases in Vietnam were studied after a rubella outbreak in 2011. The mortality associated with pulmonary hypertension was significantly high if untreated. Conducting careful cardiologic assessments and providing continuous follow-up for each patient is required.
Rubella is usually a self-limited illness; however, rubella in females during early pregnancy may result in miscarriage, fetal death, or the combination of disabilities known as congenital rubella syndrome (CRS), which is characterized by the triad of deafness, cataracts, and cardiovascular defects. Patent ductus arteriosus (PDA) is known to be the predominant cardiovascular defect; however, it is important to note that earlier studies were conducted before the availability of advanced diagnostic tests, such as cardiac catheterization and echocardiography. Because the prevalence of CRS has sharply decreased upon the introduction of rubella-containing vaccines in areas in which such advanced technology is widely available, few studies have performed precise cardiovascular assessments and regular follow-up of the patients’ clinical courses.

Between May 2009 and May 2010, we conducted a birth cohort study in Nha Trang, the capital of Khanh Hoa Province, Vietnam. We found that 29% (95% confidence interval [CI], 27%–31%) of enrolled pregnant females were rubella-specific immunoglobulin G (IgG) antibody-negative and susceptible to rubella. After that study was conducted, a large-scale rubella outbreak occurred between January and July 2011 throughout Vietnam (H.T.N. et al, unpublished observations), and many CRS cases emerged. We therefore studied these infants to characterize the clinical manifestations and outcomes of CRS. We particularly conducted cardiovascular assessments with echocardiography and followed those who had cardiovascular deficits.

METHODS

Study Setting and Period

The study site was Khanh Hoa Province in south-central Vietnam, with a population of 1.15 million in 2009. CRS surveillance was conducted between October 2011 and September 2012 at Khanh Hoa General Hospital (KHGH), the largest and only referral hospital in the province. There are 8 other small district hospitals in the province, all of which refer CRS cases to KHGH unless the cases are adequately mild. Approximately 6000 infants are delivered annually at KHGH (~33% of all births in the province and nearly 90% of all births in Nha Trang City). The survival of the enrolled CRS patients was followed by inviting them to visit KHGH every 3 months or by conducting telephone interviews until January 17, 2013, when the last-born child reached 6 months of age.

Study Subjects and Case Definition

We targeted all neonates and infants <12 months of age residing in the study area who were born at or referred to KHGH with 1 or more manifestations suggesting CRS (Fig 1), including: (1) congenital heart disease, cataract(s), glaucoma, or suspected hearing impairment, and (2) purpura, jaundice, hepatosplenomegaly, meningoorchephalitis, or microcephaly. The CRS cases were classified into confirmed, probable, and suspected cases according to the following case definitions (the Centers for Disease Control and Prevention): a confirmed case is one with any clinical manifestations of CRS confirmed on a laboratory test; a probable case is one that is not laboratory confirmed but includes either 2 of the clinical signs listed in group (1) or 1 of the clinical signs listed in group (1) and 1 of the clinical signs listed in group (2) with no evidence of any other etiology; and a suspected case is one with some compatible clinical symptoms but that does not meet the criteria for a probable case. The cases were laboratory confirmed based on the detection of either rubella-specific immunoglobulin M (IgM) antibodies on admission or rubella-specific IgG antibodies after 6 months of age.

Clinical Examinations and Laboratory Methods

Pediatricians at KHGH assessed the clinical manifestations and vital signs. All patients suspected of CRS, except for those who died soon after admission, were evaluated by using echocardiography by local ultrasonography specialists (Sonos-5500, Philips, Andover, MA). A Japanese pediatric cardiologist visited the hospital every 3 or 4 months to confirm the diagnosis and follow the patients’ cardiovascular status by using echocardiography with Doppler interrogation (Viamo SSA-640A, Toshiba, Japan). When performing a direct patient examination was not possible, the printed echocardiography images in the patient’s medical charts were checked to confirm the initial ultrasonography diagnosis. Pulmonary hypertension (PH), defined as a systolic pulmonary artery pressure (PAPs) ≥30 mm Hg, was detected based on either (1) a deformity of the left ventricle on the short-axis view in the end-systolic phase, (2) a decreased pressure gradient between the aorta and pulmonary artery estimated from the velocity of the PDA flow, or (3) an increased right ventricular pressure inferred from the tricuspid regurgitant velocity (Supplemental Fig 4). Severe PH was defined as a PAPs ≥40 mm Hg or a flat intraventricular septum on the short-axis view in the end-systolic phase. PAPs was pressure (mm Hg) + 4 × (tricuspid regurgitant velocity [meter/second]), assuming systolic systemic pressure and right atrial pressure as 80 mm Hg and 5 mm Hg, respectively. Cranial ultrasonography was also conducted to detect structural anomalies of the patients’ brains and automated auditory brain stem responses (AABR) to screen for hearing impairment (Echo-Screen estimated using the following formulas with the modified Bernoulli equation: PAPs (mm Hg) = (systolic systemic pressure − diastolic systemic pressure) * flow * 40/π * radius²).
pressure \((mm \, Hg)\) \(- \, 4 \times (velocity \, of \, PDA \, [meter/second])^2\) or \(PAPs = (right \, atrial \, II \, MAAS, \, Nippon-Koden, \, Japan).\)

Blood samples were collected on admission for measurements of the complete blood cell counts and the levels of rubella-specific IgG and IgM and, at 6 to 8 months of age, rubella-specific IgG \((SD \, BIOLINE \, Rubella \, IgG/IgM, \, STAN-DARD \, DIAGNOSTICS, \, INC., \, Korea \, or \, Elecsys, \, Roche).\) Because cerebrospinal fluid could not be obtained in most cases, meningoencephalitis was defined clinically according to the presence of abnormal neurologic findings and signs of meningeal irritation, such as neck stiffness, altered consciousness, bulging fontanels, and convulsions. A low birth weight was defined as a weight of <2500 g at birth, and preterm was defined as <37 gestational weeks.\(^{14}\) A diagram of the body weight percentiles according to the number of gestational weeks created based on the data of the subjects of a previous birth cohort study was used to identify children who were “light for gestational date” (defined as those whose body weight was below the 10th percentile).\(^{14,15}\) Microcephaly was defined as a head circumference at or below the third percentile of the mean for the infant’s gestational age.\(^{16}\) The standards of head circumference were determined based on data derived from Fenton’s growth curve for preterm infants until the patients reached a corrected gestation of 40 weeks and the World Health Organization’s growth curve for full-term infants and preterm infants whose corrected age was 40 weeks or older.\(^{17,18}\) The body weight and head circumference percentiles at 37 weeks of gestational age were used as standards for full-term infants because no precise gestational age was recorded for infants born at 37 weeks of age or more. Psychomotor development was assessed for subjects at or over 6 months of age by using investigations of anamnesis and neurologic signs. We defined a developmental delay as not holding the head up at or over 6 months of age and/or sitting up at or over 10 months of age.

**Data Analysis**

General demographic data were obtained from the Khanh Hoa Health Service. The demographic characteristics and symptoms were described by using simple tabulation. We estimated a mother’s gestational date from the date of birth and the infant’s gestational age using the following formula: (gestational date) = (date of birth) \(- \, 7 \times (gestational \, age \, [weeks]).\) The characteristics of the living and dead patients were compared by using simple tabulations and Pearson’s \(\chi^2\) test or Fisher’s exact test. The latter was used if there were more than 20% of cells with an expected value of <5 in a table.\(^{19}\) Kaplan-Meier survival estimates and the log-rank test were performed to compare the survival times of the subjects with and without PH. Cox’s proportional hazard model was used to evaluate the effects of CRS complications on survival. Correlations between the presence of PDA and premature birth or low birth weight were compared by using Fisher’s exact test to clarify their effect on PDA formation. We calculated the incidence of CRS cases per 1000 live births during the study period. The statistical analyses were conducted by using the Stata version 12.0 software program (Stata Corp, College Station, TX).

**Ethics**

Institutional Review Boards at the National Institute of Hygiene and Epidemiology, Hanoi and the Institute of Tropical Medicine, Nagasaki University approved this study. Anonymized data were used for the analyses.
RESULTS

CRS Outbreak and Incidence

From October 2011 to September 2012, a total of 38 infants who had a median age of 8.5 days (range, 0–247 days) were enrolled (Table 1). In Khanh Hoa Province, ~18,000 births occur annually. During the study period, the peak incidence of CRS in Khanh Hoa Province (7.8 per 1000 live births; 95% CI, 4.0–13.6) was in November 2011, and the incidence throughout the year (July 2011 to June 2012) was 2.1 cases per 1000 live births (95% CI, 1.5–2.9). Additionally, among 6080 births delivered in Nha Trang City in 2011, 18 patients were enrolled; therefore, the annual incidence in Nha Trang City was estimated to be 3 cases per 1000 live births (95% CI, 1.8–4.7). In Fig 2, the mothers’ estimated gestational months are shown along with the period of rubella outbreak in Vietnam (H.A.T.N. et al, unpublished observations). The mothers were estimated to have become pregnant between November 2010 and September 2011, corresponding to the period 2 months ahead of the rubella outbreak (January to November 2011).

Features of the Mothers of Infants Who Had CRS

Eighty-six percent of the mothers reported histories of fevers and rashes, mostly during the first trimester of their pregnancy. All mothers never had rubella-containing vaccines, except for 1 who stated that she had received rubella vaccine 2 months before pregnancy.

Case Enrollment and CRS Classification

The clinical manifestations, rubella-specific IgG and IgM results, and CRS classification are shown in Table 1. Echocardiography and AABR were not performed in 2 and 8 cases, respectively, because 8 patients died before the scheduled examinations (Fig 1). Two cases were categorized as suspected CRS, although they died before either echocardiography or AABR could be performed. Fourteen children (40%) were IgM-positive at enrollment and 10 were IgG-positive at or over 6 months of age. One case with negative IgM and positive IgG findings on admission was regarded as confirmed CRS because the patient was already over 6 months of age on admission. Ultimately, 25 of the 38 enrolled cases (66%) were classified as confirmed CRS.

Clinical Features and Survival of the Infants Who Had CRS

Low birth weight (71%), cardiovascular defects (72%), suspected hearing impairment (93%), hepatosplenomegaly (68%), thrombocytopenia (76%), and developmental delays (73%) were commonly found. Eighty-four percent of the patients presented with characteristic hemorrhagic purpuric eruptions, so-called “blueberry muffin baby” symptoms (Supplemental Fig 5). At enrollment, oxygen saturation was <90% in 13 patients (37%) and respiratory rate was more than 60/min in 15 (43%). Also, 11 cases (29%) showed hemoglobin levels <120 g/L and 29 (76%) had platelet counts <150 × 10^9/L (Table 1). As of January 17, 2013, 25 patients were alive and 13 (54%) had died, with a median (interquartile range [IQR]) follow-up duration of 12.2 (10.5) months. Six patients died within 1 month of enrollment; the mortality rate was 3.7/100 person-months. PH, hepatosplenomegaly, and severe thrombocytopenia were more frequently observed among the fatalities (Table 2); the hazard ratios (95% CI) for these factors were 8.33 (1.79–38.7), 7.19 (0.93–55.4), and 3.92 (1.27–12.1), respectively. A multivariate analysis was not performed owing to the small sample size. A Kaplan-Meier curve showed a significant prognostic difference between the patients with and without PH, with most deaths having occurred within 6 months of age (log-rank test, P = .001) (Fig 3).

Cardiovascular Defects in the Infants Who Had CRS

The diagnoses of cardiac defects in all examined cases are shown in Supplemental Table 3. Twenty-four (67%) cases of PDA, including 16 accompanied by PH, were detected on the first echocardiography at a median (IQR) age of 36 (76) days. Estimated PAPs, PH severity, and the consequent course of patients who had PDA are shown in Supplemental Table 4. Eleven patients diagnosed with PDA on the first echocardiography were examined 3 or 4 times in total. The median (IQR) age at the last echocardiography was 14.2 (2.4) months. The last examination showed that the PDA had naturally closed in 2 patients, remained unclosed without PH in 1 patient, remained unclosed with severe PH requiring pharmacotherapy consisting of angiotensin-converting enzyme inhibitor, diuretic, or both in 2 patients, and had been treated with catheter occlusion in 6 patients (Supplemental Table 4). Transcatheter PDA occlusion was performed for the treatment of a PDA with a left-to-right shunt that results in any of the following: congestive heart failure, failure to thrive, increased pulmonary blood flow, or an enlarged left atrium or left ventricle, provided the anatomy and patient size are suitable, according to an indication from the American Heart Association. Six patients who had an occluded PDA were in good clinical condition without PH. Among the 24 patients who had PDA, 8 were born prematurely and 19 were low birth weight infants. There were no statistically significant correlations between the presence of PDA and prematurity or low birth weight (P = .7 and P = .2, respectively).

DISCUSSION

A few studies have reported mortalities among children who have CRS, however,
TABLE 1 Manifestations and Vital Signs for Enrollment, Results of Rubella-Specific Immunoglobulin Testing, and CRS Classification For Each Case

<table>
<thead>
<tr>
<th>Pt ID</th>
<th>Age, d</th>
<th>Manifestations in Category A</th>
<th>Manifestations in Category B</th>
<th>Vital Signs at Enrollment</th>
<th>Blood Counts at Enrollment</th>
<th>Blood Counts at Enrollment</th>
<th>At Enrollment</th>
<th>Age 6 to 8 mo</th>
<th>CRS Categories</th>
<th>Age of the Last Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>C</td>
<td>P</td>
<td>He</td>
<td>Mc</td>
<td>120</td>
<td>40</td>
<td>100</td>
<td>15,700</td>
<td>141</td>
</tr>
</tbody>
</table>

COI, cutoff index; Hgb, hemoglobin (g/L); HR, heart rate (beats per minute); RR, not recorded; Pit, platelets (× 10^3/μL); Pt, patient identification number; RR, respiratory rate (per minute); SpO₂, pulse oxygen saturation (%) WBC, white blood cells (cells/μL); COI, cutoff index.

Manifestations in category A: C, heart disease; H, hepatosplenomegaly; He, hepatosplenomegaly; Me, meningoencephalitis; Mc, microcephaly (defined by Fenton and the World Health Organization); D, developmental delay.

Manifestations in category B: P, purpura; J, jaundice; He, hepatosplenomegaly; Mc, microcephaly (defined by Fenton and the World Health Organization); D, developmental delay.

Age of the last follow-up age at the time the child was last to follow-up, died, or on January 17, 2015 if the child survived, confirmed by inviting them to KHGH or by telephone.

* ABR not done.
* L, lost to follow-up.
* D, died.

+ Decision as positive or negative: +, positive; −, negative.
the direct causes of death have not been precisely described.\textsuperscript{21,22} The current study showed a high mortality rate among CRS infants. Because half of the patients died at home and 1 died a few hours after admission, it is difficult to determine the direct causes of death. However, this is the first study to demonstrate that PDA with PH and severe thrombocytopenia are significantly associated with mortality.

Oster et al, who reviewed a series of CRS studies that used cardiac catheterization (121 patients in 10 studies) or echocardiography (12 patients in 10 studies) for cardiologic evaluations, reported that 62%, 73%, and 16% had PDA, branch pulmonary artery stenosis, and pulmonary valve stenosis, respectively.\textsuperscript{5} In contrast, our first echocardiographic examinations detected PDA most frequently, whereas pulmonary valve stenosis was detected in only 2 patients, and none had branch pulmonary artery stenosis. There are several possible reasons to explain this difference. First, most of our study subjects were examined in early infancy when spontaneous PDA closing can occur and progression to pulmonary valve and pulmonary branch stenosis is not complete. Second, a diagnosis of pulmonary valve and pulmonary branch stenosis can be difficult in the presence of PH because it obscures the pressure gradient in the pulmonary artery on echocardiography. Prematurity and low birth weight are considered to be potential confounders in determining the relationship between CRS and PDA.\textsuperscript{23} However, lack of association of PDA with premature birth or low birth weight in this study indicated a pathologic role of CRS itself in PDA formation. In our study, PH was commonly associated with PDA. By repeating echocardiographic studies, we were able to demonstrate the natural history of PDA associated with CRS. It was characterized by a low likelihood of spontaneous closure and rapid progression to PH. The latter was significantly associated with mortality, likely contributing to the majority of deaths observed among the CRS patients. We did not find any

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Number of children who had CRS (n = 38) according to birth month and year and the number of mothers (n = 38) according to the month and year of rubella-like illness during pregnancy.}
\end{figure}

\begin{table}[h]
\centering
\begin{tabular}{lccc}
\hline
Characteristics & Total & Dead & Alive \\
\hline
Gender, female & 21 (55) & 7 (54) & 14 (58) \\
Preterm, <37 wk & 12 (32) & 5 (38) & 7 (28) \\
Low birth weight, <2500 g & 27 (71) & 10 (77) & 17 (68) \\
Light for gestational age, \( \leq -2 \) SD & 24 (63) & 9 (69) & 15 (60) \\
Heart defect(s) & 26/36 (72) & 10/11 (91) & 16/25 (64) \\
PDA & 24/36 (67) & 10/11 (91) & 14/25 (56) \\
PH & 16/36 (44) & 8/11 (73) & 7/25 (28) \\
Cataract(s) & 5/38 (13) & 1/13 (8) & 4/25 (16) \\
Hearing impairment & 28/30 (93) & 5/5 (100) & 23/25 (92) \\
\hline
Total & 38 & 13 & 25 \\
Gender, female & 21 (55) & 7 (54) & 14 (58) \\
Preterm, <37 wk & 12 (32) & 5 (38) & 7 (28) \\
Low birth weight, <2500 g & 27 (71) & 10 (77) & 17 (68) \\
Light for gestational age, \( \leq -2 \) SD & 24 (63) & 9 (69) & 15 (60) \\
Heart defect(s) & 26/36 (72) & 10/11 (91) & 16/25 (64) \\
PDA & 24/36 (67) & 10/11 (91) & 14/25 (56) \\
PH & 16/36 (44) & 8/11 (73) & 7/25 (28) \\
Cataract(s) & 5/38 (13) & 1/13 (8) & 4/25 (16) \\
Hearing impairment & 28/30 (93) & 5/5 (100) & 23/25 (92) \\
\hline
P values without mark “a” were calculated by Fisher’s exact test (two-tailed test). Microcephaly was diagnosed by growth curves by Fenton and the World Health Organization.
\end{tabular}
\end{table}
associations between progressive PH and CRS in previous studies. PH may be overlooked in early infantile deaths owing to its poor prognosis. PDA or pulmonary artery stenosis associated with PH may also be easily overlooked because of the absence or diminution of heart murmurs. The etiology and pathogenesis of PH associated with CRS remain unknown. We speculate, however, that both volume overload due to left-to-right shunting through the PDA and primary pulmonary vascular resistance attributable to innate vascular damage caused by congenital rubella infection are involved. With regard to the former mechanism, it is noteworthy that all patients who had PH in this study had PDA, and some of them also had atrial, ventricular, or atrioventricular septal defects; all of the patients who had double or triple shunts (n = 8) died or developed severe PH and all of the patients treated with PDA occlusion therapy (n = 7) overcame PH. Therefore, we stress the importance of conducting echocardiographic investigations for the initial assessment and follow-up of patients who have suspected CRS to predict the clinical outcome and provide appropriate clinical management, such as PDA occlusion or ligation therapy, which can cure accompanying PH.

To the best of our knowledge, this is the first prospective surveillance study of CRS in Vietnam. During a 1-year period after a rubella outbreak, we identified 38 CRS cases in Khanh Hoa, south-central Vietnam. In this study, the monthly incidence of CRS was 2.1 per 1000 live births, with a peak of 7.8 per 1000 live births. The incidence of CRS determined in this study may have been underestimated because we enrolled only infants who had obvious manifestations and did not include those who died in other small district hospitals soon after delivery. The incidence in Nha Trang City was 3.0 per 1000 live births, which we assumed to be more accurate. The number of CRS cases in this study was comparable to the findings of previous epidemic reports from Oman, Ghana, Panama, and Russia (0.7, 0.8, 2.2, and 3.5 per 1000 live births during epidemics, respectively), and a CRS incidence of 2.3 (95% CI, 2.1–2.6) cases per 1000 live births in Vietnam estimated by modeling.

Unfortunately, hemodynamic status in each patient was not precisely recorded. Heart rates, respiratory rates, and oxygen saturation were recorded only at enrollment. Blood pressure was not measured owing to a lack of sphygmomanometers for infants. Consequently, we missed opportunities to comprehensively monitor their cardiorespiratory status by using such parameters in combination with echocardiography. Furthermore, we performed neither virus isolation nor polymerase chain reaction for rubella virus in this study, although they are desirable for more precise diagnosis and in view of infection control in countries with better resources.

Despite the aforementioned limitations, we believe that this study will contribute to improving the understanding of clinical manifestations and outcomes of CRS, a tragic but preventable disease.

CONCLUSIONS

PH-associated mortality is high among infants who have CRS in Vietnam. Providing proper assessments, continuous follow-up, and timely intervention for cardiovascular defects is critical for the management of CRS patients. Echocardiography is of diagnostic and prognostic value and can support better clinical management of CRS, even in a developing country setting.

ACKNOWLEDGMENTS

This was a collaborative research effort between Nagasaki University (Japan), NIHE (Vietnam), Khanh Hoa Provincial Public Health Service (Vietnam), and KHGH (Vietnam). We thank all participants and those who cooperated in this study in both Vietnam and Japan.
REFERENCES

20. Wong KC. Chi squared test versus Fisher’s exact test. Hong Kong Med J. 2011;17(S):427
41. ICD-10 Version. 2010. Available at: http://apps.who/int/cla...385–396
Mortality Associated With Pulmonary Hypertension in Congenital Rubella Syndrome
Michiko Toizumi, Hideki Motomura, Hien Minh Vo, Kensuke Takahashi, Enga Pham, Hien Anh Thi Nguyen, Tho Huu Le, Masahiro Hashizume, Koya Ariyoshi, Duc Anh Dang, Hiroyuki Moriuchi and Lay-Myint Yoshida

*Pediatrics* 2014;134;e519
DOI: 10.1542/peds.2013-4184 originally published online July 7, 2014;

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/134/2/e519">http://pediatrics.aappublications.org/content/134/2/e519</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplementary Material</td>
<td>Supplementary material can be found at: <a href="http://pediatrics.aappublications.org/content/suppl/2014/07/24/peds.2013-4184.DCSupplemental">http://pediatrics.aappublications.org/content/suppl/2014/07/24/peds.2013-4184.DCSupplemental</a></td>
</tr>
<tr>
<td>References</td>
<td>This article cites 22 articles, 5 of which you can access for free at: <a href="http://pediatrics.aappublications.org/content/134/2/e519.full#ref-list-1">http://pediatrics.aappublications.org/content/134/2/e519.full#ref-list-1</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s):</td>
</tr>
<tr>
<td></td>
<td><strong>Infectious Disease</strong> <a href="http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub">http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub</a></td>
</tr>
<tr>
<td></td>
<td><strong>International Child Health</strong> <a href="http://classic.pediatrics.aappublications.org/cgi/collection/international_child_health_sub">http://classic.pediatrics.aappublications.org/cgi/collection/international_child_health_sub</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="https://shop.aap.org/licensing-permissions/">https://shop.aap.org/licensing-permissions/</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://classic.pediatrics.aappublications.org/content/reprints">http://classic.pediatrics.aappublications.org/content/reprints</a></td>
</tr>
</tbody>
</table>
Mortality Associated With Pulmonary Hypertension in Congenital Rubella Syndrome

Michiko Toizumi, Hideki Motomura, Hien Minh Vo, Kensuke Takahashi, Enga Pham, Hien Anh Thi Nguyen, Tho Huu Le, Masahiro Hashizume, Koya Ariyoshi, Duc Anh Dang, Hiroyuki Moriuchi and Lay-Myint Yoshida

*Pediatrics* 2014;134:e519

DOI: 10.1542/peds.2013-4184 originally published online July 7, 2014;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://pediatrics.aappublications.org/content/134/2/e519